

The QUEST initiative anemia study in transplant patients: rationale and study protocol

Wim Van Biesen¹, Francesco Locatelli²,
Mateus Martins Prata³, Jean Pierre Wauters⁴,
Alicja Dębska-Ślizień⁵, Joan M. Mauri⁶,
Kaj Metsärinne⁷, Gabriel Mircescu⁸,
Kostas C. Siamopoulos⁹, Vianda S. Stel¹⁰, Eric Will¹¹,
Lucia Del Vecchio¹², Carmine Zoccali¹³, Kitty J. Jager¹⁰

For the QUEST Anemia Study Group*

¹ Renal Division, University Hospital Ghent, Ghent - Belgium

² Division of Nephrology and Dialysis, Alessandro Manzoni Hospital, Lecco - Italy

³ Division of Nephrology, Santa Maria University Hospital, University of Lisbon, Lisbon - Portugal

⁴ Division of Nephrology and Hypertension, University Hospital of Bern, Bern - Switzerland

⁵ Department of Nephrology, Transplantation and Internal Medicine, Medical University of Gdańsk, Gdańsk - Poland

⁶ Division of Nephrology, University Hospital Dr. J. Trueta, Girona - Spain

⁷ Department of Nephrology, Turku University Central Hospital, Turku - Finland

⁸ "Carol Davila" University of Medicine and Pharmacy, Bucharest - Romania

⁹ Nephrology Department, Medical School, University of Ioannina, Ioannina - Greece

¹⁰ ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, Amsterdam - The Netherlands

¹¹ Honorary Renal Physician, Leeds Teaching Hospitals NHS Trust, Leeds - United Kingdom

¹² Department of Hypertension and Preventive Nephrology, IRCCS Multimedica, Sesto San Giovanni, Milan - Italy

¹³ CNR-IBIM, Clinical Epidemiology and Physiopathology of Renal Disease and Hypertension & Unit of Nephrology, Dialysis and Renal Transplant, Ospedali Riuniti, Reggio Calabria - Italy

INTRODUCTION

Do we need an observational study on the management of anemia in transplant patients?

In contrast to the situation for patients on dialysis, there are only limited data available regarding the management of anemia in long-term kidney-transplanted patients (1).

It can be anticipated that a substantial part of these transplant patients fall in the chronic kidney disease (CKD) stages 3, 4 and 5, and therefore that some degree of renal anemia is prevalent.

The Transplant European Survey on Anemia Management (TRESAM) (2) revealed that more than one third of the transplant patients had some degree of anemia. It is quite likely that, besides the renal factors causing anemia (3), other factors also, such as chronic inflammation and the use of certain

immunosuppressive agents, contribute to the enhanced risk of anemia in these patients (4).

The registration of patients planned by the QUEST (Quality European STudies) project would thus deliver new information on the general performance of renal function in long-term transplant patients and also on the specific domain of the impact of CKD on anemia in transplant patients, and its management.

Although the data on the need for, and the use of, erythropoiesis-stimulating agents (ESAs) in transplant patients are scarce (1), it would not come as a surprise to see a higher degree of underachievement of anemia management in this patient group compared with other clinical settings for patients with CKD.

To start with, many physicians and patients are reluctant to admit that the renal function of a graft is suboptimal, especially if it is declining over time. Talking about starting treat-

ment with ESAs might ring a bell in the patient's mind that "something is going wrong", and it is not unlikely that both patients and physicians will try to delay this moment as long as possible. It has been described that in anemic transplant patients, only a minority receive ESAs (2, 5).

Second, iron management might be more problematic in this patient group, as easy access to intravenous iron is not available as it is in dialysis patients, which might also lead to incomplete correction of anemia. Molnar et al found (5) that iron deficiency was an important predictor of anemia in renal transplant patients, even after correction for kidney function and chronic inflammation. Winkelmayr et al (6) found that the percentage of hypochromic red blood cells rather than anemia per se was related to mortality and graft loss. Third, it might be that financial reimbursement for ESAs is cumbersome in some regions or countries.

Anemia is related to cardiovascular comorbidity and other bad outcomes in CKD patients. In addition, the available evidence indicates that anemia is an early indicator of bad prognosis, both for graft and patient survival (7) and also for cardiovascular morbidity (8) in transplant patients.

A well-performed observational study is thus urgently needed to obtain more information on the management of anemia in renal transplant patients, and its relation with outcome.

STUDY PROTOCOL FOR PREVALENCE AND MANAGEMENT OF ANEMIA IN RENAL TRANSPLANT PATIENTS: A MULTICENTER CROSS-SECTIONAL EUROPEAN STUDY

Introduction

Anemia is a common and well-recognized problem in patients with CKD. Over the last 2 decades, treatment of renal anemia has been substantially improved by the introduction of ESAs. Data on the management of anemia in transplant patients are scarce, and the available evidence seems to indicate that transplant patients, despite being in at least CKD stage 3, are mostly not considered as CKD patients. Physicians have a low awareness of renal anemia in these patients and/or are reluctant to start treatment with ESAs.

Renal transplant patients have several concomitant and cumulative reasons for being anemic, and it is not surprising that the prevalence of anemia in transplant patients is reported to be quite high. However, prevalence and best treatment of anemia in renal transplant patients has not

yet been fully elucidated on a large scale. In particular, little is known about causes of ESA hyporesponsiveness in this setting. In view of the potential effect of anemia on the outcome of both patient and graft survival, and many deleterious posttransplant factors (medications, chronic inflammation, declining renal function etc) the present investigation could give important new insights.

Aim of the project

1. Identify the relative contribution of the different factors that hamper optimal correction of anemia in renal transplant patients by determining
 - the prevalence and distribution of CKD stages 3, 4 and 5 in a large European renal transplant patient population;
 - the prevalence and distribution of anemia in a large European renal transplant patient population;
 - the degree of anemia correction achieved and dosage patterns of ESAs;
 - the prevalence of ESA hyporesponsiveness (i.e., >300 U/kg per week) (considered as a continuous and as a categorical variable) and its underlying causes;
 - the factors that may explain differences in anemia correction and/or ESA hyporesponsiveness at a national, regional and/or center level.
2. Set up an instrument that will allow us to improve anemia management at the individual patient and center level.

It is anticipated that, as part of a quality improvement program, the return of the results to the participating centers will also allow each of them to optimize their anemia management at the levels of individual patient and center care. Therefore, the same evaluation will be conducted after 1 year in the same participating centers.

Study design

This project is a cross-sectional study of all renal transplant patients followed in the participating units and will register the following:

- demographic, clinical and hematologic data;
- renal function (measured creatinine clearance and/or estimated glomerular filtration rate [eGFR]);
- immunosuppressive regimens;
- use of ESAs;
- iron management and administration;
- other parameters potentially related to ESA hyporesponsiveness.

After 12 months, the same evaluation will be repeated in the same centers according to the same inclusion and exclusion criteria.

Center and patient inclusion criteria

Countries and centers to be included in the study will be selected aiming at a wide geographical coverage that is balanced across Europe, and starting with those countries represented in the working group. The target number for inclusion of patients is 3,500.

The working group members will act as study counsellors at the national level and verify the time schedule at the participating units.

In addition, a part-time study coordinator and data manager will be hired.

Participating centers will receive 10 euros per completed patient file.

All centers which participate should include all surviving renal transplant patients at the time of their last visit during the preceding 12 months.

Patients should have undergone a transplant at least 1 year previously, to avoid the interference of acute problems related to the act of transplantation.

Local ethics committee approval and patient informed consent forms may be requested depending on the national and/or local regulations. In cases where an informed consent form is mandatory at the local level, the number of patients refusing to participate should not exceed 10% of the total number of treated patients. If this percentage is exceeded, another center should be asked to participate.

Study protocol

Parameters to register:

A. Individual patient data

1. Demographic data

- Sex
- Ethnicity
- Age
- Height and weight to calculate Body Mass Index (BMI) and Body Surface Area (BSA) adjusted GFR
- Type of underlying renal disease (according to EDTA Registry coding)
- Diabetes as cause of renal failure: yes/no
- Posttransplant-related diabetes: yes/no
- Time since transplant: months
- Type of transplant: living or cadaver
- Number of present transplant: first, second ...

2. Biological and clinical data

- Hemoglobin (Hb)
- Reticulocyte count
- Iron store parameters: ferritin, transferrin saturation
- Renal function (either measured creatinine clearance and/or estimated GFR based on the IDMS (Isotope Dilution Mass Spectrometry) traceable simplified Modification of Diet in Renal Disease [MDRD] formula)
- Serum albumin
- C-reactive protein (CRP)
- Intact parathormone (PTH) level
- Serologic hepatitis B and C status
- Aggravating clinical factors during the preceding 3 months: infection, malignancy, episodes of bleeding, surgery, hospitalization ...
- Delayed graft function after transplant: yes/no (need for dialysis)

3. Therapeutic data

- Immunosuppression: daily doses at the time of Hb determination
- Use of ESA: yes/no
 1. agent: epoetin-alpha, epoetin-beta, darbepoetin, other ...
 2. total administered dose during the 4 weeks preceding the biological control (raw units/weights; a conversion factor for darbepoetin-alpha will be applied centrally)
 3. administration route: subcutaneous or intravenous
 4. administration frequency: days/month ...
 5. start of ESA: <3 months, between 3-6 months, >6 months before data collection
 6. time after transplant, creatinine level (or eGFR), Hb concentration at start of ESA
- Iron administration (in the extended data set): yes/no
 1. agent: saccharate, dextran, gluconate, other ...
 2. total administered dose over the 4 weeks preceding the biological control
 3. administration route: intravenous vs. peroral
 4. administration frequency: days/month, on demand
- (Oral) anticoagulants: yes/no
- Platelet inhibitors: yes/no
- Angiotensin-converting enzyme inhibitors and/or sartanes: yes/no

B. Center data

1. Transplant center policy

- Recommended type and mode of ESA administration
 - Type of guidelines followed
 - Type of iron storage parameters and dosage; iron administration and policy in interval prior to serum iron parameter sampling
 - Management of anemia parameters on a daily basis: nephrologist, transplant consultant nurse, dedicated nurse
2. Use of management software tools and/or database
 3. National/regional policy for ESA prescription
 4. National/regional policy for ESA reimbursement

Statistical analysis

Statistical analysis will include

1. descriptive analysis of the data, at the individual center, country and European levels (mean and/or median, with 25th and 75th percentiles, as appropriate);
2. comparisons in relevant subgroups according to sex, country, cadaveric vs. living graft, delayed graft function, immunosuppressive regimen, ESA agent, administration route of ESA etc. These analyses will be performed by t-test, Mann-Whitney test or 1-way ANOVA, as applicable ;
3. univariate and multivariate regression analysis of different continuous variables (Hb, ESA dose, age, months on dialysis, months after transplant, iron parameters, CRP, renal function, PTH) with ESA dose, and Hb levels achieved.

To avoid interference with "loading dose" problems,

patients treated with ESA for less than 6 months will be analyzed separately.

For all statistical investigations and their results, it will be kept in mind that these should be considered as hypotheses generating associations, and that these may not be causal.

APPENDIX

*QUEST Anemia Study Group: C. Zoccali and K. Jager (QUEST co-chairs), F. Locatelli (chair), M. Martins Prata (co-chair), J.P. Wauters (co-chair), L. Del Vecchio (secretary), W. Van Biesen (secretary), A. Dębska-Ślizień, J.M. Mauri, K. Metsärinne, G. Mircescu, K.C. Siamopoulos, V.S. Stel, E. Will (members).

ACKNOWLEDGEMENTS

The Quest project is funded by ERA-EDTA. The Anemia Study is supported by an unrestricted grant from Amgen.

Conflict of interest statement: None declared.

Address for correspondence:

Kitty J. Jager
ERA-EDTA Registry
Department of Medical Informatics
Academic Medical Center
P.O. Box 22700
1100 DE Amsterdam, The Netherlands
k.j.jager@amc.uva.nl; Wim.vanbiesen@ugent.be

REFERENCES

1. Vanrenterghem Y. Prevalence and management of anaemia in transplant patients. *Nephrol Dial Transplant* 2002; 17 (Suppl 1): S47.
2. Vanrenterghem Y, Ponticelli C, Morales JM, Abramowicz D, Baboolal K, Eklund B, Kliem V, Legendre C, Morais Sarmiento AL, Vincenti F. Prevalence and management of anemia in renal transplant recipients: A European survey. *Am J Transplant* 2003; 3: 835-45.
3. Yorgin PD, Scandling JD, Belson A, Sanchez J, Alexander SR, Andreoni KA. Late post-transplant anemia in adult renal transplant recipients: An under-recognized problem? *Am J Transplant* 2002; 2: 429-35.
4. Muirhead N. Erythropoietin and renal transplantation. *Kidney Int* 1999; 55 (Suppl 69): S86-92.
5. Molnar MZ, Novak M, Ambrus C, Kovacs A, Pap J, Rempert A, Szeifert L, Mucsi I. Anemia in kidney transplanted patients. *Clin Transplant* 2005; 19: 825-33.
6. Winkelmayer WC, Lorenz M, Kramar R, Horl WH, Sunder-Plassmann G. Percentage of hypochromic red blood cells is an independent risk factor for mortality in kidney transplant recipients. *Am J Transplant* 2004; 4: 2075-81.
7. Molnar MZ, Czira M, Ambrus C, Szeifert L, Szentkiralyi A, Beko G, Rosivall L, Rempert A, Novak M, Mucsi I. Anemia is associated with mortality in kidney-transplanted patients: A prospective cohort study. *Am J Transplant* 2007; 7: 818-24.
8. Rigatto C, Foley R, Jeffery J, Negrijn C, Tribula C, Parfrey P. Electrocardiographic left ventricular hypertrophy in renal transplant recipients: Prognostic value and impact of blood pressure and anemia. *J Am Soc Nephrol* 2003; 14: 462-8.

© Società Italiana di Nefrologia